

University of Groningen

Pulmonary vasodilator therapy as treatment for patients with a Fontan circulation

Ridderbos, Floris-Jan S; Hagdorn, Quint A J; Berger, Rolf Mf

Published in:
Pulmonary circulation

DOI:
[10.1177/2045894018811148](https://doi.org/10.1177/2045894018811148)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Ridderbos, F-J. S., Hagdorn, Q. A. J., & Berger, R. M. (2018). Pulmonary vasodilator therapy as treatment for patients with a Fontan circulation: the Emperor's new clothes? *Pulmonary circulation*, 8(4).
<https://doi.org/10.1177/2045894018811148>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Pulmonary vasodilator therapy as treatment for patients with a Fontan circulation: the Emperor's new clothes?

Floris-Jan S. Ridderbos , Quint A.J. Hagdorn and Rolf M.F. Berger

Department of Pediatric Cardiology, Center for Congenital Heart Diseases, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Pulmonary Circulation 2018; 8(4) 1–2

DOI: 10.1177/2045894018811148

Dear Editor

With great interest we read the recent article by Wang et al. in *Pulmonary Circulation* presenting a meta-analysis on the efficacy and safety of pulmonary vasodilator therapy in patients with a Fontan circulation.¹ We commend the authors with this thorough attempt to provide an overview of the available evidence on this important and controversial topic. The authors report that they have performed a meta-analysis of randomized controlled trials (RCTs) and conclude that pulmonary vasodilator therapy, although not reducing mortality, improves peak oxygen consumption (pVO_2), hemodynamics, and 6-min walking distance (6MWD) and reduces NYHA functional class statistically significantly based on nine studies.

After thorough assessment of the manuscript and considering the increased interest for the use of pulmonary vasodilator therapy in Fontan patients, we feel the necessity to express our concerns regarding the claims and conclusions drawn by the authors. Meta-analyses can be a valuable tool to assess systematically available information from different studies in order to derive conclusions from the total body of research. However, it cannot provide evidence that is not there. The current meta-analysis includes extremely heterogeneous data from a limited number of studies with significant clinical and methodological diversity. When substantial heterogeneity exists, pooling data from multiple trials and presenting a single summary estimate can be misleading and should be avoided.²

There are several important points to take into consideration when interpreting this meta-analysis. First, concerning inclusion criteria; two of the included studies are not RCTs (one retrospective design and one prospective design with a historical cohort control group) and thus in fact do not fulfill the authors' inclusion criteria of RCT-only studies.^{3,4} Without these two studies there is only one RCT reporting on mean pulmonary artery pressure (mPAP)⁵ and only RCT data from one medical center on mortality,^{5,6} making a meta-analysis on hemodynamics and mortality a futile attempt.

As a consequence, no meaningful conclusions can be drawn considering mPAP and mortality. Furthermore, data and conclusions regarding 6MWD outcomes are from two studies from one and the same center, with identical treatment protocols and likely to have overlapping patient populations. Therefore, a meta-analysis applied on these data can be questioned.^{5,6}

Second, concerning study population and time of treatment, four of the included studies concern pediatric patients only and, more importantly, three of these study the effect of pulmonary vasodilators in the immediate perioperative period of the Fontan-procedure.^{3,4,6} In contrast, the remaining five studies include adult patients at mid-term to long-term follow-up after the Fontan procedure. In our opinion, these studies cannot be compared side-by-side since the pathophysiology and efficacy variables are completely different in both situations. Further, the meta-analysis includes studies assessing the effect of a single drug dose and those assessing the effect of maintenance therapy. When pooling studies with such heterogeneity in patient population, timing, and duration of treatment, one compares apples to oranges.

Third, regarding pVO_2 , of the five studies, only three studies found a small increase in pVO_2 (1.4, 1.7, 1.8 mL/kg/min) whereas the two other studies did not show any improvement (0 and –1 mL/kg/min pVO_2). Most importantly, the study reporting a 1.8 mL/kg/min increase was actually a cross-sectional study including a single dose of sildenafil between two cardiopulmonary exercise tests (CPETs) on the same day.⁷ This study (with an assigned weight of 67%) mainly determined the pooled estimate outcome of 1.42 mL/kg/min improvement in pVO_2 .

Corresponding author:

Floris-Jan S. Ridderbos, Department of Pediatric Cardiology, Center for Congenital Heart Diseases, Beatrix Children's Hospital, University Medical Center Groningen, P.O. Box 30.001, internal zip code CA41, 9700 RB Groningen, The Netherlands.
Email: f.j.s.ridderbos@umcg.nl



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

© The Author(s) 2018.
Article reuse guidelines:
sagepub.com/journals-permissions
journals.sagepub.com/home/pul



Although these results are all interesting and of individual value, one should critically question whether the reported effect sizes on pVO_2 are valid and represent a clinically significant improvement. In this journal,⁸ Lammers and Humpl speak their minds and express the hope that the results from the presented meta-analysis will encourage clinicians to consider pulmonary vasodilator therapy for selected Fontan patients, irrespective of the current absence of a recommendation in the ESC guidelines.⁹ In the perspective, outlined above, we feel this encouragement is premature and not supported by the currently available data: the evidence is simply not there (yet).

One must keep in mind that pulmonary vasodilator therapy, originally approved for the treatment of pulmonary arterial hypertension (PAH), is aimed to stimulate endothelial-derived vaso-relaxation factors resulting in relaxation of the vascular smooth muscle cells (VSMCs) leading to vasodilation which reduces pulmonary vascular resistance. Pulmonary vascular remodeling in long-term Fontan patients has been shown to have a strikingly different pattern compared to that in PAH. The latter pattern is characterized by VSMC proliferation, whereas in Fontan patients a pattern of progressive medial atrophy with a loss of VSMCs and eccentric luminal fibrosis has been observed.¹⁰ These observations challenge the concept that the beneficial effects of pulmonary vasodilator therapy in PAH can be translated to patients with a lasting Fontan circulation.

At best, the current meta-analysis may support the suggestion for beneficial short-term effects of pulmonary vasodilator therapy in selected patients with a Fontan circulation. The conclusions as drawn by the authors highly overrate the available evidence which is misleading. In the near future, the results from the ongoing RUBATO (NCT03153137) and FUEL (NCT02741115) trials may provide more evidence on the efficacy of pulmonary vasodilator therapy in Fontan patients. Given the paucity of therapeutic options for the failing Fontan patient, it may be tempting to surrender to hopeful or wishful thinking. However, for now we want to warn to stay critical on this matter in order not

to misperceive pulmonary vasodilator therapy for Fontan patients as the proverbial new clothes of the Emperor.

ORCID iD

Floris-Jan S. Ridderbos  <http://orcid.org/0000-0001-5101-219X>

References

1. Wang W, Hu X, Liao W, et al. EXPRESS: The efficacy and safety of pulmonary vasodilators in patients with fontan circulation: a meta-analysis of randomized-controlled trials. *Pulm Circ* 2018. Epub ahead of print. doi: 10.1177/2045894018790450.
2. Thompson SG and Pocock SJ. Can meta-analyses be trusted? *Lancet* 1991; 338(8775): 1127–1130.
3. Mendoza A, Albert L, Belda S, et al. Pulmonary vasodilator therapy and early postoperative outcome after modified Fontan operation. *Cardiol Young* 2014; 25: 1136–1140.
4. Giordano R, Palma G, Poli V, et al. First experience with sildenafil after Fontan operation: Short-term outcomes. *J Cardiovasc Med* 2015; 16(8): 552–555.
5. Shang XK, Lu R, Zhang X, et al. Efficacy of Bosentan in patients after Fontan procedures: a double-blind, randomized controlled trial. *J Huazhong Univ Sci Technol Med Sci* 2016; 36(4): 534–540.
6. Shang X, Li Y, Liu M, et al. [Efficacy of endothelin receptor antagonist bosentan on the long-term prognosis in patients after Fontan operation]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2013; 41(12): 1025–1028.
7. Giardini A, Balducci A, Specchia S, et al. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. *Eur Heart J*. 2008; 29(13): 1681–1687.
8. Lammers AE and Humpl T. Use of pulmonary vasodilators in Fontan patients: A useful strategy to improve functional status and delay transplantation? *Pulm Circ* 2018; 8(3): 1–2.
9. Baumgartner H, Bonhoeffer P, De Groot NMS, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010; 31(23): 2915–2957.
10. Ridderbos FS, Wolff D, Timmer A, et al. Adverse pulmonary vascular remodeling in the Fontan circulation. *J Hear Lung Transplant* 2015; 34(3): 404–413.